REMARKS/ARGUMENTS

Applicants provide herewith an amendment to the specification and claims as described above. Amendment of the terms "Alzheimer's" and "Parkinson's" in paragraph **0093**, the word "Permanent" in paragraph **0102** and the numbers listed in paragraph **0193** are to correct typographical errors, and support for these corrections is self-evident. Registered trademark® or trademark™ designations have been added to company names in paragraphs **0102** and **0144**. Support for other amendments to the specification and claims is discussed elsewhere herein. Applicants submit that no new matter has been added to the application specification or claims by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Office Action dated February 10, 2005, included:

- status of the Restriction/Election Requirement;
- indication of priority;
- information disclosure statement acknowledgement;
- objections to the specification;
- rejections for alleged indefiniteness (35 U.S.C. §112, second paragraph);
- rejections for alleged anticipation (35 U.S.C. §102); and
- rejections for alleged obviousness (35 U.S.C. §103).

Applicants traverse all rejections and objections, to the extent that they may be applied to the amended claims, for the reasons noted herein. The present Response with Amendment is fully responsive to each of the Examiner's points, and Applicants respectfully request reconsideration of the claims in view of the amendments and remarks herein.

THE STATUS OF THE CLAIMS

Claims **1-50** are pending and claims **51-57** are cancelled with entry of this amendment. Claim **35** is amended herein. These amendments to the claims introduce no new matter and support is replete throughout the specification as originally filed. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

THE ELECTION/RESTRICTION REQUIREMENT

Applicants thank the Examiner for their reconsideration of the Requirement for Restriction/Election. Applicants acknowledge the combination of the claims in Groups I and II to form a single group for examination, consisting of claims **1-50**. Pursuant to a restriction requirement made final, Applicants cancel claims **51-57** with entry of this amendment. Applicants reserve the right to file subsequent applications claiming the canceled subject matter encompassed by claims **51-57** or similar claims, and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

THE INFORMATION DISCLOSURE STATEMENT

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statements (Forms 1449) submitted on December 1, 2003 and October 29, 2004. Applicants point out that two Supplemental Information Disclosure Statements (and two Forms 1449) have subsequently been filed in the USPTO, namely on February 24, 2005 and March 29, 2005, after the mailing of the first Office Action. Applicants respectfully request consideration of these references.

OBJECTIONS TO THE SPECIFICATION

The Examiner objected to the specification because the specification allegedly contains embedded hyperlinks or other forms of browser-executable code, which are impermissible. Furthermore, the Examiner required a determination of whether the subject matter referenced by the various web-addresses is essential or non-essential subject matter, and further required deletion of the hyperlink, and if necessary, amendment of the specification to include the essential subject matter.

The Applicants understand that as a policy matter, the USPTO does not wish to publish patents that include hyperlinkable citations. Thus, in this regard, Applicants note that the issue of objection is whether the website citations are browser executable or not.

The web addresses found in paragraphs **0093, 0102, 0103, 0133, 0138** and **0144** are for the purpose of referencing non-essential subject matter that illustrate the general state of the art. To comply with the Examiner's objection, Applicants have either deleted the internet citation, or amended the internet citation to render them non browser executable. If the

Examiner would prefer a different non browser executable citation format, Applicants will gladly comply with any alternative format the Examiner suggests. In light of these amendments to the specification, Applicants respectfully request withdrawal of this objection.

35 U.S.C. §112, SECOND PARAGRAPH

Claims **35-36** were rejected under 35 U.S.C. §112, second paragraph, as indefinite because of alleged ambiguity in the term "comprising" alleged lack of clarity in claim **35**. The Examiner states that it is unclear whether the steps provided in claim **35** are alternative steps or additional steps, and further, which of the claim **1** and **25** method steps are being limited.

Applicants respectfully disagree. However, solely for the purpose of advancing the prosecution of the present application, and without acquiescing to the Examiner's argument, Applicants have amended claim **35**. This amendment is for the purpose of removing any perceived lack of clarity in the claim. Applicants have also incorporated the Examiner's suggestion to include the phrase "further comprising." The currently amended claim **35** now refers to the "plurality of defined sequence probes" as recited in claims **1** and **25**, and clarifies that the "determining" step further limits step (e) in claim **1** and step (c) in claim **25**.

To further clarify the claim language, the term "expression" was changed to "detectable signal" to provide a better defined referent, as the phase "detectable signal" is found in step (d) of claim **1** and step (b) of claim **25**. The use of two different probe detectable signals corresponding to a housekeeping gene probe and a target gene probe, as well as the relative quantitation of those signals, is taught throughout the specification. See, *e.g.*, paragraph **0021** and the section starting at paragraph **0158**.

In view of the currently amended claim **35**, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. §102

The claims are novel over Thomas *et al.*

Claims **1-13, 15, 17, 21-27, 33-39, 42-45, 49** and **50** were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Thomas *et al., Molecular Pharmacology* 60(6):1189-

1194 (2001). Applicants respectfully disagree, and traverse this rejection. Arguments herein apply to the amended forms of claims.

In order for a reference to anticipate a claim, the reference must teach each and every element of the claim (MPEP 2131). Applicants assert that the Examiner has not met this requirement. Applicants point out that the Examiner has failed to recognize one of the critical defining features of the invention. This aspect of the invention is specifically recited in the two independent claims, **1** and **25**. Because Thomas *et al.* do not teach this claimed element, none of the claims are anticipated by Thomas *et al.*

The present invention provides compositions and methods for screening compound libraries and for quantitating expression products from biological samples. The two independent claims at issue in the present Office Action (claims **1** and **25**) utilize microarray-based technology to facilitate high throughput analysis of biological samples. The classical microarray configuration, as known in the art, is described in the specification at paragraph **0008**:

> Nucleic acid microarrays are available, having the benefit of assaying for sample hybridization to a large number of probes in a highly parallel fashion. They can be used for quantitation of mRNA expression levels [. . .]. These arrays comprise short DNA probes, such as PCR products, oligonucleotides, or cDNA products fixed onto a solid surface, which can then be used in a hybridization reaction with a target sample, generally a whole cell extract [. . .], cellular RNA sample, or cDNA sample corresponding to cellular RNAs.

As described in paragraph **0008**, the classical microarray formats known in the art (*e.g.*, Thomas *et al.*) typically involve the arrangement of large numbers (*e.g.*, hundreds or thousands) of defined "bait" sequences spatially arrayed on a solid phase surface, each in a unique addressable location, followed by application of a labeled nucleic acid sample (typically, a collection of RNA or cDNA) to the microarray. This typical configuration permits the analysis of gene expression for numerous query sequences (the probes) in a single biological sample. Multiple replicate arrays can be assembled for testing multiple samples. Unfortunately, this approach is cumbersome and prohibitively expensive when used for the purpose of screening large numbers of nucleic acid samples (such as compound library screening).

In contrast, as described in the specification, the claimed invention uses a novel variation of the classical microarray configuration. This novel approach is emphasized throughout the specification, and is most clearly described in paragraphs **0036-0038** and

0216-0218. These paragraphs explain that the invention involves screening compound libraries (*e.g.*, analyzing nucleic acid samples derived from treated cells) by "flipping" the standard microarray paradigm. The arrays used with the invention comprise nucleic acid samples fixed onto the solid phase support surface, which is then used in a hybridization reaction with a soluble phase nucleic acid probe of defined sequence.

In other words, the present invention uses a microarray format that inverts the normal sample/probe relationship. In this novel configuration, the experimental nucleic acid samples are assembled into an array (fixed to the solid phase). Multiple gene specific probes are then hybridized to these sample arrays. Thus, in the present invention, the nucleic acid samples are placed on the solid surface and the defined known sequences of interest are in solution. Classical microarrays differentiate between the genes being monitored by assigning a unique spatial address to each of the gene specific probes on the microarray surface. The methods described herein flip the classical format, and distinguish between different gene specific probes by differential labeling of the soluble phase probes (*e.g.*, by labeling different probes with fluorescent labels that can be uniquely identified by their absorption/emission properties). In this novel format as described in the specification, it is the nucleic acid sample that is assigned a unique spatial placement (not the defined sequence probes).

This novel aspect of the invention is reflected in the independent claims **1** and **25**. Step (c) in claim 1 recites "arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA samples to produce a nucleic acid array," and further recites step (d) comprising "hybridizing a plurality of defined sequence probes [. . .] to the nucleic acid array." Similarly, step (a) in claim 25 recites, in part, "providing at least one nucleic acid array comprising a plurality of amplified nucleic acids corresponding to a plurality of expressed RNA samples," followed by step (b) which recites in part "hybridizing a plurality of defined sequence probes."

The Examiner describes where support is allegedly found in Thomas *et al.* for each of the steps of independent claim **1** (Office Action pages 5-6). It is unclear to the Applicants if the Examiner intended their arguments to extend equally to independent claim **25**. Although independent claims **1** and **25** have some shared steps and common technical features, each must be examined on its own merits. Applicants remarks herein will assume that it was the

Examiner's intention that the arguments made to reject independent claim **1** apply equally to independent claim **25**.

The Examiner has mischaracterized the present invention. The Examiner states that step (c) in claim **1** reciting "arraying a plurality of nucleic acids" is anticipated by Thomas *et al.* on page 1190, 1st column, in the section **cDNA Microarray Construction and Analysis**. Applicants disagree. In its entirety, step (c) in claim **1** reads "arraying a plurality of nucleic acids *corresponding to the plurality of expressed RNA samples to produce a nucleic acid array*." Applicants point out that the nucleic acids used to form the arrays of the invention are derived from the RNA samples isolated from the biological samples that were previously exposed to the compound library. In contrast, the microarray described in Thomas *et al.* is constructed using the traditional arrangement of arraying defined sequence EST cDNA probes onto the solid support. Thomas *et al.* states "Each cDNA clone was spotted four times on each slide for replicate analysis." Furthermore, Thomas *et al.* also state that total RNA was isolated from the treated cells and then used to make poly-A RNA. This poly-A sample RNA was then used in reverse transcription reactions to generate Cy3 or Cy5 labeled nucleic acid that is used in hybridization on the microarray (see Thomas *et al.* on page 1190, 1st column).

Thomas *et al.* use a classical microarray approach in the methods described in that reference. Thomas *et al.* do not describe an inverted microarray configuration as used in the invention, where the sample nucleic acids area affixed to the solid phase and the defined sequence probes are labeled and are in the soluble phase. Since Thomas *et al.* fails to teach each element of the claimed invention (as claimed in independent claims **1** and **25**), Thomas *et al.* does not anticipate claims **1** or **25**. The Examiner also pointed to subject matter in Thomas *et al.* that allegedly further rendered dependent claims **2-13, 15, 17, 21-24, 26, 27, 33--39, 42-45, 49** and **50** anticipated. However, if an independent claim is novel, so must each claim that depends upon the independent claim also be novel, as each dependent claim contains all of the limitations found in the independent claim. The Examiner's pointing to additional support in Thomas *et al.* for alleged anticipation of the dependent claims is insufficient to render any of the claims anticipated. Because Thomas *et al.* do not teach each element of the claimed invention, Applicants request withdrawal of this rejection.

The claims are novel over Mohanlal.

Claims **1-15, 17-26, 30-34, 37-45 and 50** were rejected under 35 U.S.C. §102(a) or (e) as allegedly anticipated by International Application Publication WO 02/40717 to Mohanlal, published May 23, 2002. Applicants disagree, and traverse the rejection.

In a situation analogous to the Thomas *et al.* 102(a) rejection described above, Applicants believe that the Examiner has similarly mischaracterized the invention and failed to recognize one of the defining features of the claimed invention, namely, the use of an inverted microarray format. This aspect is not taught in Mohanlal. Because Mohanlal does not teach this feature of the invention, none of the claims are anticipated by Mohanlal.

As described above, the classical microarray formats known in the art typically involve spatially arrayed large numbers (*e.g.*, hundreds or thousands) of probe sequences affixed to a solid phase surface (*e.g.*, a microarray slide), followed by application of a sample consisting of a labeled pool of nucleic acids derived from a source sample (*e.g.*, total RNA or poly-A RNA isolated from treated cells or tissues). The labeled components from the nucleic acid sample hybridize to the spatially arrayed probes that have been affixed to the array solid surface.

In contrast, as described in the specification, the claimed invention uses a non-traditional microarray configuration, where the normal sample/probe relationship is inverted. In this novel configuration, a nucleic acid pool derived from treated samples is affixed onto the solid phase support surface. This array is then probed (*i.e.*, used in a hybridization reaction) with a soluble phase nucleic acid probe(s) of defined sequence. This novel approach is emphasized throughout the specification, and is most clearly described in paragraphs **0036-0038** and **0216-0218**. This aspect of the invention is reflected in independent claims **1** and **25**, as described above.

The Examiner describes where support is allegedly found in Mohanlal for the steps of claims **1** and **25**, collectively resulting in the alleged anticipation of independent claims **1** and **25**. The Examiner states that support for step (c) comprising "arraying a plurality of nucleic acids corresponding to the plurality of expressed RNA to produce a nucleic acid array" can be found on, for example, page 12, lines 13-16; and page 17, lines 4-6. Applicants point out that Mohanlal discloses only classical microarray configurations. See, *e.g.*, Mohanlal on page 26, lines 12-15:

> Hybridization patterns of probes prepared from the subtracted libraries I-VI are used to create our own customized microarrays displaying subtracted sequences. This is followed by hybridization of probes of all individual patient samples onto the microarrays displaying the subtracted libraries.

See also page 26, lines 18-20, "Commercially available microarrays can also be used to examine differentially expressed genes, using a hybridization reaction between the sequences on the microarray and a fluorescent sample (36)."

These methods described by Mohanlal are classical microarray configurations. Nowhere does Mohanlal describe an inverted microarray configuration as used in the present invention and recited in independent claims **1** and **25**. The Examiner has mischaracterized the present invention and failed to recognize the "inverted microarray" feature of the invention. Although the Examiner points out passages that allegedly teach some limited aspects of the invention in both the independent and dependent claims, that is insufficient to render the Mohanlal reference as anticipatory, since Mohanlal is lacking description of an inverted microarray format. Furthermore, the Examiner's assessment that Mohanlal teaches the hybridization format as used in the claimed invention (at pages 12, 17, 18 and 19, as stated by the Examiner) is incorrect, for the reasons discussed above. Since Mohanlal fails to teach each element of the claimed invention, the reference does not anticipate the claimed invention, and Applicants request withdrawal of this rejection.

35 U.S.C. §103(a)

The claims are novel over Thomas *et al.* in view of the general state of the art.

Claims **16** and **18-20** were rejected under 35 U.S.C. §103(a) as allegedly obvious over the explicit teachings and general guidance in Thomas *et al.* and in view of the general state of the art. Applicants disagree, and traverse the rejection.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference(s) must teach all of the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure (M.P.E.P § 2142-2143).

More specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the

claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The Examiner alleges that Thomas *et al.* provides general teaching that that would motivate one of ordinary skill in the art to generate as many as 70,000 RNA samples, derived from treatments using as many as 70,000 of the chemicals known in commerce at the time the application was filed, thereby rendering claims **18-20** obvious. Furthermore, the Examiner also alleges that the use of prokaryotic samples in high throughput microarray technology (claim **16**) would also be obvious to one of skill in the art given the well-established nature of microarray technology at the time the application was filed. Applicants disagree.

The Examiner's arguments presuppose that Thomas *et al.* also renders claim **1** as obvious (or anticipated), since claims **16** and **18-20** are dependent on claim **1**, and thereby contain all of the limitations of claim **1**. As discussed in the sections above, Thomas *et al.* is deficient and is incapable of rendering claim **1** anticipated (or obvious). Thomas *et al.* teaches a classical microarray paradigm. In contrast, the invention uses an inverted microarray configuration that flips the usual sample/probe relationship. Thomas *et al.* does not teach this limitation, nor is it within the scope of what one of skill in the art might be motivated to try at the time the application was filed, even in view of the state of the art. Since Thomas *et al.* in view of the general state of the art is incapable of teaching all the limitations of claims **16** and **18-20**, the Examiner has not made a *prima facie* case for obviousness, and the Applicants request that this rejection be withdrawn.

The claims are novel over Thomas *et al.* in view of Wang *et al.*

Claims **40** and **41** were rejected under 35 U.S.C. §103(a) as allegedly obvious over Thomas *et al.* in view of US Patent No. 5,922,617, issued July 13, 1999 to Wang and Li. Applicants disagree, and traverse the rejection. As noted above, a *prima facie* case of obviousness requires, among other things, that the prior art references must teach all of the limitations of the claims (M.P.E.P § 2142-2143). The Examiner has not met this requirement.

The Examiner states that Thomas *et al.* employs two-dimensional glass microarrays. The Examiner states that Wang and Li teach microarray substrates consisting of silicone, magnetic beads, and other materials. Furthermore, the Examiner alleges that a wide array of additional substrates were known in the microarray technologies at the time of the invention was made, and one of skill in the art would have been motivated to use of these solid substrate materials, as evidenced by Wang and Li. Applicants disagree.

The Examiner's arguments presuppose that Thomas *et al.* (with or without the combination of Wang and Li) also renders claim **1, 25** and **38** as obvious (or anticipated), since claims **40** and **41** are ultimately dependent on claim **1** or **25**, and thereby contain all of the limitations of claim **1** or **25**. As discussed in the sections above, Thomas *et al.* is deficient and is incapable of rendering claim **1** or **25** anticipated (or obvious). This deficiency is not remedied by combination with Wang and Li. Thomas *et al.* teaches a classical microarray paradigm. In contrast, the invention uses an inverted microarray configuration that flips the usual sample/probe relationship. Neither Thomas *et al.* nor Wand and Li teach this limitation. Since Thomas *et al.* in view of Wang and Li is incapable of teaching all the limitations of claims **40** and **41**, the Examiner has not made a *prima facie* case for obviousness, and the Applicants request that this rejection be withdrawn.

The claims are novel over Mohanlal in view of Chenchik *et al.*

Claims **16, 35, 36** and **46-49** were rejected under 35 U.S.C. §103(a) as allegedly obvious over International Application Publication WO 02/40717 to Mohanlal, published May 23, 2002 in view of International Application Publication WO 99/35289 to Chenchik and Siebert, published July 15, 1999. Applicants disagree, and traverse the rejection. Arguments herein apply to the amended forms of claims.

A *prima facie* case of obviousness requires, among other things, that the prior art references must teach all of the limitations of the claims (M.P.E.P § 2142-2143). The Examiner has not met this requirement.

The Examiner states that Mohanlal does not explicitly teach the use of prokaryotic samples, the use of housekeeping genes as normalization controls, the use of multiplex PCR using gene specific primers, or the use of universal priming sequences in conjunction with gene specific primers. The Examiner also states that Mohanlal does not teach the use of amplifiable signal element detection mechanisms as recited in claims **46-48**.

The Examiner states that Chenchik and Siebert disclose the use of housekeeping genes as hybridization normalization controls and also disclose a variety of fluorescent labels and probe signal amplification mechanisms. The Examiner also states that the use of microarrays was a well established art at the time the invention was made, and such features as high throughput, the analysis of eukaryotic or prokaryotic samples, the use of control nucleic acids in hybridization normalization, and diverse labeling schemes would have been known to one skilled in the art, as evidenced by Chenchik and Siebert.

The Examiner alleges that it would have been prima facie obvious to combine the teachings of Mohanlal with Chenchik and Siebert, and in view of the level of ordinary skill in the art, to arrive at the claimed invention, namely, claims **16, 35, 36** and **46-49**.

Applicants disagree. Claims **16, 35, 36** and **46-49** also contain the limitations of those claims on which they are dependent, namely claims **1** or **25**. As discussed thoroughly in the sections above, Mohanlal is deficient and is incapable of rendering claim **1** or **25** anticipated (or obvious). This deficiency is not remedied by combination with Chenchik and Siebert. Neither Mohanlal nor Chenchik and Siebert teach an inverted microarray configuration where the nucleic acid sample is fixed to the solid phase and the defined-sequence probes are in the soluble phase. Since Mohanlal in view of Chenchik and Siebert is incapable of teaching all the limitations of claims **16, 35, 36** and **46-49**, the Examiner has not made a *prima facie* case for obviousness, and the Applicants request that this rejection be withdrawn.

The claims are novel over Mohanlal in view of Shuber.

Claims **29** and **29** were rejected under 35 U.S.C. §103(a) as allegedly obvious over International Application Publication WO 02/40717 to Mohanlal, published May 23, 2002 in view of US Patent Application 5,882,856 to Shuber, published March 16, 1999. Applicants disagree, and traverse the rejection.

A *prima facie* case of obviousness requires, among other things, that the prior art references must teach all of the limitations of the claims (M.P.E.P § 2142-2143). The Examiner has not met this requirement.

The Examiner states that Mohanlal does not explicitly teach multiplex amplification using gene specific primers, and further, primers comprising universal sequences. The Examiner states that Shuber teaches multiplex amplification methods that use universal

priming sequences, and alleges that it would have been *prima facie* obvious to combine the teachings of Mohanlal with Shuber to arrive at the claimed invention, namely, claims **28** and **29**.

Applicants disagree. Claims **28** and **29** also contain the limitations of those claims on which they are dependent, namely claims **1** or **25**. As discussed thoroughly above, Mohanlal is deficient and is incapable of rendering claim **1** or **25** anticipated (or obvious). This deficiency is not remedied by combination with Shuber. Neither Mohanlal nor Shuber teach an inverted microarray configuration where the nucleic acid sample is fixed to the solid phase and the defined-sequence probes are in the soluble phase. Since Mohanlal in view of Shuber is incapable of teaching all the limitations of claims **28** and **29**, the Examiner has not made a *prima facie* case for obviousness, and the Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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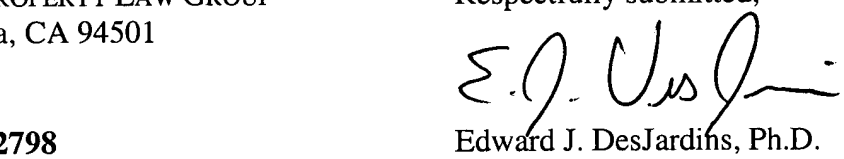
Respectfully submitted,



Edward J. DesJardins, Ph.D.
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Attachments:

1) a transmittal sheet; and
2) a receipt acknowledgement postcard.